REMARKS

In the Final Action dated November 1, 2007, Claims 1-14 are pending. Claims 5 and 8-14 are withdrawn from consideration. Claims 1-4 and 6-7 are examined and rejected as allegedly obvious under 35 U.S.C. §103(a) over McIntosh et al. (U.S. Patent No. 6,767,896 B1) ("the '896 patent") in view of Jones et al. (U.S. 2005/0271589 A1) ("the '589 publication").

This Response addresses the Examiner's rejection. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Specifically, Applicants provide herewith a Declaration of Dr. Richard J. Lewis, in support of patentability of the claimed invention. Applicants have also added new claims 15-16, which are drawn specifically to the conotoxin peptide having the amino acid sequence of SEQ ID NO: 4 or salt, ester or amide thereof (claim 15) and to the C-terminus amidated conotoxin peptide having the amino acid sequence of SEQ ID NO: 4. SEQ ID NO: 4 is the elected amino acid sequence. The language, "salt, ester or amide thereof", finds support in the specification and in claim 1. The C-terminus amidated peptide having the amino acid sequence of SEQ ID NO: 4 is disclosed in the specification, e.g., on page 29, lines 21-23, which is also referred to as "Xen2174" in the specification. No new matter is introduced by new claims 15-16.

Turning to the rejection, the Examiner is of the opinion that the claimed conotoxin peptide, particularly, the χ-conotoxin peptide having the sequence,

pGluGlyValCysCysGlyTyrLysLeuCysHisHypCys (SEQ ID NO: 4),

is obvious in light of the '896 patent, alone or in combination with the '589 publication. Specifically, the Examiner states on page 4 of the Office Action:

> "[T]he issue presented is whether one of ordinary skill in the art at the time of the invention would have been motivated by the

teachings/suggestions of McIntosh et al. alone or in view of Jones et al. to select pGly in position 1 of same conotoxin peptide (over native Asn) of McIntosh et al. … from a Markush group of ONLY three amino acid options (Asn, Gln, pGlu) – 1 of which, Asn, is the native amino acid." (Emphasis in original).

To reach his conclusion, the Examiner has apparently specifically selected the Mar1 peptide sequence of the '896 patent, and the N-terminal amino acid position of this peptide, as the basis of modification in order to arrive at instant SEQ ID NO: 4. As discussed in detail below, Applicants respectfully submit that neither the '896 patent nor the '589 publication teaches or suggests to the skilled artisan to select the Mar1 peptide, and then select its N-terminal amino acid position for further modification. Further, Applicants respectfully submit that the references do not teach or suggest substituting the N-terminal Asn of Mar1 with pGlu. As further discussed below, Applicants respectfully submit that the limited disclosure of pGlu in the '896 patent relates to peptides, specifically Q819, which have Gln as its native N-terminal residue.

Applicants provide first a brief review of the '896 patent. The '896 patent discloses conotoxin peptides characterized by a general formula I, as set out in SEQ ID NO: 1:

Xaa-Xaa_0-Xaa_1-Cys-Cys-Gly-Xaa_2-Xaa_3-Xaa_4-Cys-Xaa_5-Xaa_6-Cys-Xaa_7 (SEQ ID NO: 1)

According to the '896 patent, each of Xaa, Xaa_1, Xaa_2, Xaa_3, Xaa_4, Xaa_5, Xaa_6, and Xaa_7 (i.e., nine out of the fourteen amino acid positions) can be selected from a group of possible amino acid residues. The '896 patent further discloses several sub-generic peptides that fall "within general formula I":

Asn-Gly-Val-Cys-Cys-Gly-Xaa_1-Xaa_2 -Leu-Cys-His-Xaa_3 -Cys (SEQ ID NO:2);

Gly-Val-Cys-Cys-Gly- Xaa_1-Xaa_2-Leu-Cys-His-Xaa_3-Cys (SEQ ID NO:3);

Gly-Ile-Cys-Cys-Gly-Val-Ser-Phe-Cys- Xaa_1- Xaa_3 -Cys (SEQ ID NO:4);

Ala-Cys-Cys-Gly- Xaa_1-Xaa_2-Leu-Cys-Ser-Xaa_3 -Cys (SEQ ID NO:5);

Xaa_4-Thr-Cys-Cys-Gly-Xaa_1-Arg -Met- Cys-Val- Xaa_3-Cys-Gly (SEQ ID NO:6);

Ser-Thr-Cys-Cys-Gly-Phe-Xaa_2-Met-Cys-Ile- Xaa_3-Cys-Arg (SEQ ID NO:7).

Each of Xaa_1, Xaa_2, Xaa_3, Xaa_4 in SEQ ID NOS: 2-7 is also selectable from a group of amino acids. When a certain amino acid is selected for each of the Xaa's in SEQ ID NOS: 2-7, the following six specific conotoxin peptides are derived, which, according to the '896 patent, represent native conotoxin peptides from various Conus species (see col. 4 and col. 22 of the '896 patent):

Mar 1: Asn-Gly-Val-Cys-Cys-Gly-Tyr-Lys-Leu-Cys-His-Hyp-Cys

Mar 2: Gly-Val-Cys-Cys-Gly-Tyr-Lys-Leu-Cys-His-Hyp-Cys

U036: Gly-Ile-Cys-Cys-Gly-Val-Ser-Phe-Cys-Tyr-Hyp -Cys

Q818: Ala-Cys-Cys-Gly-Tyr-Lys-Leu-Cys-Ser-Hyp -Cys

Q819: Gln-Thr-Cys-Cys-Gly-Tyr-Arg-Met-Cys-Val-Hyp-Cys-Gly

Q820: Ser-Thr-Cys-Cys-Gly-Phe-Lys-Met-Cys-Ile-Hyp-Cys-Arg

According to the Examiner,

> "As to the modified conotoxin peptide formula of McIntosh et al., the native conotoxin peptide options are fixed as the first option of each Xaa option of the formula. And specifically, as to Xaa1 (Asn, Gln, pGlu) and Xaa6 (Pro, hydroxyl-Pro (e.g., 4-hydroxyproline) or g-Hyp) – there are ONLY three amino acid options thereto, one of which is the native amino acid. As to the latter, hydroxyl-Pro is a known modified amino acid version of Pro. It is the Xaa1 position that is primarily at issue here and discussed in detail below." page 3, bottom paragraph of the Office Action (emphasis in original).

By "formula", it is believed that the Examiner is referring to formula I of the '896 patent. Applicants respectfully submit that there is no teaching in the '896 patent for a preference to select native amino acid options over non-native amino acid options. Further, as discussed above, the '896 patent discloses six (6) specific native conotoxin peptides (Table on col. 4 of the '896 patent). Although these six specific peptides all fall within general formula I, the amino

acid sequences of these peptides vary significantly. Thus, even if one were to select each Xaa option of formula I based on amino acids found in a native conotoxin peptide, there are multiple options to select. For example, among the choices provided for each of the Xaa's in formula I, there are three to five possible amino acid options for each of the following seven Xaa positions, all representing amino acids found in a native conotoxin peptide:

Xaa: des-Xaa, Asn, Gln
Xaa0: des-Xaa, Gly, Ala, Ser
Xaa1: Val, Ala, Thr, Ile
Xaa2: Phe, Tyr, Val
Xaa3: Lys, Arg, Ser
Xaa4: Leu, Phe, Met
Xaa5: His, Tyr, Ser, Ile, Val

Therefore, it is unclear to Applicants why the Examiner has decided to ignore the various possibilities for all the Xaa's, and to focus on only Xaa1 and Xaa6. In fact, even if one were to select amino acids based on the first choice given for each Xaa's in the '896 patent, one would arrive at the sequence, Val-Cys-Cys-Gly-Phe-Lys-Leu-Cys-His-Hyp-Cys, which would miss two amino acids (pGlu-Gly) at the N-terminus and have a "Phe" instead of "Tyr", as compared to SEQ ID NO: 4 of the '704 application. Applicants' position is also supported by Dr. Lewis's Declaration. See Paragraphs 5-10 of the Declaration.

In any event, for reasons unclear to Applicants, the Examiner has specifically selected the Mar1 peptide sequence of the '896 patent, and the N-terminal amino acid position of this peptide, as the basis of further modification in order to arrive at instant SEQ ID NO: 4.

Applicants respectfully submit that there is no teaching or suggestion in the '896 patent for the selection of the Mar1 peptide, or any other of the six native peptides, as a basis for further modification. As stated in the Declaration, Paragraph 11:

> "Stability has been one of the key advantages of disulfide-rich conotoxins, having evolved to remain intact in venom for months and perhaps longer

> before being deployed in prey capture and defense. The chi conotoxins such as Mar1 are highly networked with four of 13 residues involved in disulfide bridges, and like other disulfide-rich conotoxins, stability was considered to be an already inherent advantage of this family. The '896 patent does not disclose any need or advantage for further modifying any of the six native peptides."

Furthermore, assuming that one were motivated to further modify Mar1, there is no teaching or suggestion in the '896 patent for specifically selecting the N-terminal residue of Mar1 (Asn) as a basis for further modification. Based on formula I, and theoretically, seven out of the thirteen amino acids of Mar1 can be substituted with a different amino acid residue, which again, can be selected from a group of amino acid options. Moreover, the '896 patent discloses Mar1 as falling within the sub-generic sequence of SEQ ID NO: 2. Based on SEQ ID NO: 2, and theoretically, three amino acid positions of Mar1 can be modified, each position having several choices of amino acid residues. However, none of these three amino acid positions is the N-terminal residue.

Furthermore, Applicants respectfully submit that the disclosure of pGlu in the '896 patent is limited. Specifically, there are only two references to pGlu in the '896 patent. The first reference appears in the context of formula I (col. 3, line 23), where pGlu is listed as one of four possible choices for the N-terminal amino acid of formula I. Again, this formula will not give rise to SEQ ID NO: 4 of the '704 application unless each of the remaining eight Xaa residues is specifically selected to correspond to the native Mar 1 or Mar 2 amino acid residues. The second reference to pGlu appears on column 4, line 16-17 of the '896 patent. Here, pGlu is disclosed as a possible alternative for Gln as the N-terminal residue of SEQ ID NO: 6. SEQ ID NO: 6 of the '896 patent differs from instant SEQ ID NO: 4 in several other amino acid positions.

Therefore, it is Applicant's position that the limited disclosure of pGlu in the '869 patent relates to peptides, specifically Q819, which have Gln as its native N-terminal residue.

The disclosure relating to pGlu in the '589 publication is also made in the context of peptide having a native Gln as the N-terminal residue. See Paragraph 0014 of the '589 publication. Applicants respectfully submit that such limited disclosures in the references do not suggest to the skilled artisan to make an Asn-pGlu substitution in Mar1, because (1) the Gln-pGlu substitution occurs naturally, whereas the Asn-Gln substitution was never documented and is considered to be a non-conservative substitution; and (2) Q819 of the '896 patent and the peptides of the '589 publication belong to classes of conotoxins distinct from Mar1, and therefore the Gln-pGlu substitution suggested in the references would not be expected to be relevant or applicable to Mar1.

In support of Applicants' position, the Examiner's attention is directed to Paragraphs 15-19 of the Declaration, where Dr. Lewis established that while pGlu forms naturally from Glu and Gln, no example of the Asn substitution by pGlu is identified in extensive literature searching, and instant SEQ ID NO: 4 represents the first example of such a substitution. Further, the replacement of a native N-terminal Glu or Gln by pGlu, or the addition of pGlu to the N-terminus, do not necessarily provide a genuine advantage. Moreover, the Asn substitution by pGlu is considered to be a non-conservative substitution.

In addition, Applicants direct the Examiner's attention to Paragraphs 20-23 of the Declaration, where Dr. Lewis discussed that the disclosures of the '589 publication and the '869 patent with respect to pGLu are made in the context of peptides that belong to a different class and have a native Gln as the N-terminal residue, and would not be understood to be applicable to peptides having a different N-terminal residue such as Asn, or to peptides of a different class (such as Mar1).

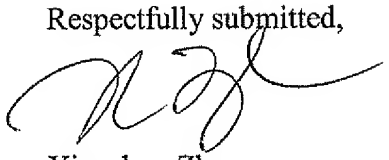
Applicants respectfully submit that SEQ ID NO: 4 of the present application represents the first example of a conotoxin peptide having a Asn-pGlu substitution. Not only this substitution was not suggested anywhere in the cited prior art, the superior properties of the resulting peptide are also unexpected. In Paragraphs 24-28 of the Declaration, Dr. Lewis described the results of a number of experiments, which demonstrate that Xen2174 (the C-terminal amidated SEQ ID NO: 4) provides clear and unprecedented advantages over SEQ ID NO: 1 (also known as Mar1 or χ-MrIA) and other chi conotoxins including, notably, conotoxins that differ from SEQ ID NO: 4 only by their N-terminal residues. See Paragraph 27 of the Declaration.

Therefore, consistent with Dr. Lewis' conclusion, Applicants respectfully submit that that there is no suggestion in the '896 patent or the '589 publication for selecting the Mar1 peptide, and then selecting the N-terminal amino acid position of this peptide, as the basis for further modification. Further, there is no suggestion in the '896 patent or the '589 publication for substituting Asn of Mar1 with pGlu. The present application provides the first example of a peptide having an Asn to pGlu substitution, which has been shown to possess superior and unexpected properties.

Accordingly, the obviousness rejection based on the combination of the '896 patent and the '589 publication is overcome. Withdrawal of the rejection is respectfully requested.

In view of the foregoing remarks, it is firmly believed that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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